A Safety and Efficacy Trial of Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected with the GM-CSF Gene in Combination with Adjuvant Chemoradiotherapy for the Treatment of Adenocarcinoma of the Pancreas

Non-technical Abstract

Cancer of the pancreas is the tenth leading cause of cancer in the United States with an estimated incidence of 29,500 new cases in 1999. It is also one of the most lethal malignancies and is currently the fifth leading cause of cancer death with an estimated number of deaths in 1999 similar to the incidence rate. The death rate in pancreatic cancer is exceeded only by lung, colorectal, breast, and prostate cancer. Despite recent advances in the overall understanding of pancreatic cancer, improved imaging techniques to identify disease at an earlier stage, improved surgical techniques, and the use of adjuvant therapy (chemotherapy and radiation therapy that is given in addition to surgery when patients are expected to have a high likelihood of recurrence), the 1-year survival is still on the order of 20% with a median survival of 15 to 19 months for disease amenable to surgery and a 5-year survival of approximately 3% for all stages of pancreatic cancer combined. Only one drug, Gemcitabine, is currently approved for this disease. This drug was approved by the FDA based on a significant improvement in quality of life only.

Chemotherapy and radiation are used as adjuvant therapy in pancreatic cancer. This study, to be conducted by Johns Hopkins Hospital, Baltimore, MD, will use chemoradiation and an additional adjuvant, immunotherapy. Immunotherapy is a type of treatment for cancer based on the idea that the immune system (the system in the body that fights infection) can be activated to destroy cancer cells that have grown undetected. A vaccine is a way of delivering an antigen (something that stimulates the immune system) to the immune system so that it recognizes the antigen as foreign and destroys any cells bearing that antigen.

Allogeneic pancreatic tumor cell vaccine consists of two types of pancreatic tumor cells developed from the tumor cells of patients with pancreatic cancer. The human GM-CSF gene was used to genetically modify the pancreatic cells. GM-CSF, a substance made by the body that helps the immune system recognize a tumor and destroy it. The vaccine cells were irradiated to prevent them from growing or dividing. The cells themselves are **not** radioactive. The cells are stored frozen until the day of vaccination. The total number of cells in each vaccination will be 50,000,000, divided into six injections, given in the thighs and arms. The choice of six injections for each vaccination is based on the volume of the vaccination and a finding that the body has a better chance to respond to the vaccine if it is injected into a number of different areas.

Following surgical removal of the pancreas, 60 patients with stage 1, 2, or 3 adenocarcinoma of the pancreas will receive a combination of 5-FU-based chemotherapy and local radiation in sequence with the pancreatic tumor vaccine. Patients will receive the first vaccination 8 to 10 weeks following surgery. Sixteen days after vaccination, patients will begin a 26-week course of adjuvant radiation and chemotherapy at Johns

Hopkins. Four to eight weeks following completion of the last cycle, eligible patients will receive two additional vaccinations at 1-month intervals. Patients who continue to remain disease-free will receive a fourth "booster" vaccination 3 months following the third vaccination.

Blood samples to measure GM-CSF levels will be taken at several time points: For the second and third vaccines, samples will be taken on the day of vaccination and then every day for 3 days. For the fourth vaccination samples will be taken on the day of vaccination and then every day for 4 days. Blood samples to evaluate the safety of the vaccinations will be taken on the day of vaccine administration and then once a week for 1 month following each vaccination. Blood samples may be taken near the patient's home and sent to Johns Hopkins for testing.

During the first study of this vaccine in pancreatic cancer, local symptoms were experienced at the vaccine site, such as swelling and redness, around 2 to 7 days after vaccination. In this study, if the patient's vaccination site shows swelling over 1 cm in diameter, a skin biopsy will be taken. The skin biopsy will be evaluated to determine to what types of cells are important to the immune response. Based on preclinical data and data from the first study, the biopsy will be taken on day 3, and possibly on day 7, after vaccination. Other tests and evaluations include history and physical examination, vital signs, CT of the abdomen, chest, and pelvis, prevaccination biopsy, and a skin test for delayed-type hypersensitivity (DTH) that is like a PPD test and involves injecting the patient's own tumor cells after they have been irradiated to prevent growth and division. The purpose of the DTH test is to evaluate whether the patient has developed a systemic immune response against their cancer. Data from the first study suggests that there is a correlation between this DTH response to autologous tumor and a clinical response.

We began recruiting patients into a phase II study January 30, 2002 (New Protocol Amendment was submitted in July 10, 2001 (Amendment BB-IND 7136/012). The phase II study is a safety and efficacy trial of $5x10^8$ lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene in combination with adjuvant chemoradiotherapy for the treatment of adenocarcinoma of the pancreas. Since that time we have consented 36 patients. Of the 36 patients, 25 were found to be eligible for the study and received at least one vaccination. Of the 25 patients that received at least one vaccination, 15 (62%) remain on study with no evidence of disease recurrence. Six subjects have now received more than one vaccination. Of the five subjects that have received three vaccinations, 80% remain disease-free. One patient is currently disease free after receiving the second vaccination. Five subjects who had received one vaccination only had disease progression before receiving the second vaccination. One subject has had local recurrence after three months after receiving the third vaccination.

All patients experienced local vaccine related adverse events including redness, swelling, and pruritus. Other less frequent side effects observed that may be related to the vaccine include: headache, low grade fever, and diarrhea.

Three serious adverse events were recorded during this reporting period. Two subjects who received one vaccination are off study without evidence of recurrence. One patient with pre-existing coronary artery disease had a coronary event during radiation and chemotherapy treatment and died of this event. A second patient is recovering from a 5-FU toxicity related to adjuvant chemotherapy. One subject was hospitalized three months after receiving the third vaccination for pain control as a result of disease recurrence. These serious adverse events were not related to the vaccine therapy.